

The opinion in support of the decision being entered today was not written
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte STEPHEN P. EISENBERG, CASEY C. CASE
GEORGE N. COX III, ANDREW JAMIESON
and EDWARD J. REBAR

Appeal No. 2006-0189
Application No. 09/825,242

ON BRIEF



Before MILLS, GRIMES, and GREEN, Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

DECISION ON APPEAL

This appeal involves claims to a method of designing and making a zinc finger protein that binds to a selected target site, which the examiner has rejected as obvious.

We have jurisdiction under 35 U.S.C. § 134. We reverse.

Background

"Zinc finger proteins (ZFPs) are proteins that can bind to DNA in a sequence-specific manner. . . . A single finger domain is about 30 amino acids in length. . . . To date, over 10,000 zinc finger sequences have been identified in several thousand known or putative transcription factors." Specification, page 1.

“The x-ray crystal structure of Zif268, a three-finger domain from a murine transcription factor, has been solved in complex with a cognate DNA-sequence. . . . The structure suggests that each finger interacts independently with DNA over 3 base-pair intervals, with side-chains at positions -1, 2, 3 and 6 on each recognition helix making contacts with their respective DNA triplet subsites.” Id.

“The structure of the Zif268-DNA complex also suggested that the DNA sequence specificity of a zinc finger protein might be altered by making amino acid substitutions at the four helix positions (-1, 2, 3 and 6) on each of the zinc finger recognition helices.” Page 2.

The specification describes “methods of designing zinc finger proteins that bind to a preselected target site. . . . The methods of design use a database containing information about previously characterized zinc finger proteins. This information includes names or other designations of previously characterized zinc finger proteins, the amino acid sequence of their component fingers, and the nucleotide triplets bound by each finger of the proteins. Information in the database is accessed using an algorithm that allows one to select fingers from different previous designs for combination in a novel zinc finger protein having specificity for a chosen target site.” Page 13.

Discussion

1. Claim construction

Claims 35, 40, 48, 49, and 53 are on appeal. Claims 37, 38, 41-43, and 52 are also pending; the examiner has indicated that these claims are allowable (Examiner's Answer, page 2).

Claim 35 is representative and reads as follows:

35. A method of producing a zinc finger protein or a nucleic acid encoding the same, comprising:

(a) providing a database comprising designations for a plurality of precharacterized zinc finger proteins, each protein comprising at least first, second and third fingers, and subdesignations for each of the three fingers of each of the zinc finger proteins, wherein at least one protein in the database has a third finger that is different from the third finger of at least one other protein in the database; a corresponding nucleic acid sequence for each zinc finger protein, each sequence comprising at least first, second and third triplets specifically bound by the at least first, second and third fingers respectively in each zinc finger protein, the first, second and third triplets being arranged in the nucleic acid sequence (3'-5') in the same respective order as the first, second and third fingers are arranged in the zinc finger protein (N-terminal to C-terminal);

(b) providing a preselected target site for design of a zinc finger protein, the target site comprising contiguous first, second and third triplets in a 3'-5' order,

(c) for the first, second and third triplet in the target site, identifying first, second and third sets of zinc finger protein(s) in the database, the first set comprising zinc finger protein(s) comprising a finger specifically binding to the first triplet in the target site, the second set comprising zinc finger protein(s) comprising a finger specifically binding to the second triplet in the target site, the third set comprising zinc finger protein(s) comprising a finger specifically binding to the third triplet in the target site;

(d) outputting designations and subdesignations of the zinc finger proteins in the first, second, and third sets identified in step (c); and

(e) producing (i) a zinc finger protein that binds to the target site comprising a first finger from a zinc finger protein from the first set, a second finger from a zinc finger protein from the second set, and a third finger from a zinc finger protein from the third set, or (ii) a nucleic acid encoding the zinc finger protein.

Thus, claim 35 is directed to a method of making a zinc finger protein that has been designed to bind to a specific target site. The method comprises providing a database that includes designations for zinc finger proteins that each comprise at least three zinc fingers. The claim requires that the database also include subdesignations for each of the three zinc fingers in each protein, as well as the complete (9-nucleotide)

nucleic acid sequence bound by the three zinc fingers in each of the zinc finger proteins.

Claim 35 requires the further steps of providing a target site for the zinc finger protein being designed (the target site being of a size that will be bound by three zinc fingers); identifying three sets of zinc finger proteins in the database, each of which includes proteins that include a zinc finger that will bind to one-third of the intended target site; outputting the designations for the proteins and zinc fingers in each of the three identified sets; and producing a zinc finger protein that includes the zinc fingers identified as binding to part of the intended target site.

2. Obviousness

The examiner rejected claims 35, 40, 48, 49, and 53 under 35 U.S.C. § 103 as obvious in view of Choo (PNAS),¹ Choo (Nature)² and Corbi.³ The examiner characterized Choo (Nature) as

show[ing] a method of designing a zinc finger protein that binds to a BCR-ABL recombined oncogene target site. . . . [E]ach triplet of the intended binding site (shown in figure 1) was used to screen a randomized zinc finger library. . . . Selected zinc fingers that bound a desired triplet were combined into a set of three finger zinc finger proteins.

Examiner's Answer, page 4. The examiner acknowledged that Choo (Nature) "does not show the extent of precharacterization of the zinc finger proteins in the randomized zinc finger library or a database of the randomized zinc finger library." Id., page 5.

¹ Choo et al., "Toward a code for the interactions of zinc fingers with DNA: Selection of randomized fingers displayed on phage," Proc. Natl. Acad. Sci. USA, Vol. 91, pp. 11163-11167 (1994).

² Choo et al., "In vivo repression by a site-specific DNA-binding protein designed against an oncogenic sequence," Nature, Vol. 372, pp. 642-645 (1994).

³ Corbi et al., "Synthesis of a new zinc finger peptide; comparison of its 'code' deduced and 'CASTing' derived binding sites," FEBS Letters, Vol. 417, pp. 71-74 (1997).

The examiner relied on Choo (PNAS) for teaching “a phage library comprising zinc finger genes in which the middle of three fingers is randomized. . . [and] show[ing] in figure 2 a database of selected and characterized library members.” Id. The examiner relied on Corbi for its teaching of a zinc finger protein having three fingers, and the target site bound by the protein. Id.

The examiner concluded that

[i]t would have been obvious to a person of ordinary skill in the art at the time the invention was made to precharacterize the selected random library members of Choo et al. [(Nature)] to any desired extent to aid in further analysis of selected library members because Choo et al. [(PNAS)] shows such analysis in figure 2 and pages 11164-11167. It would have been further obvious to record such characterizations in a database as shown in Choo et al. [(PNAS)] figure 2. . . . It would have been further obvious to add other known zinc finger proteins and their binding specificities such as the Mago zinc finger protein of Corbi et al. to further increase the diversity of choices available in the database.

Id., page 6.

Appellants argue that, “even assuming arguendo that the cited references are properly combined, the references neither individually or in combination provide any disclosure of a database comprising designations for a plurality of three-finger zinc finger proteins, subdesignations for each of three fingers for each zinc finger protein, and their corresponding target nucleic acid sequences, as specified in claim[s] 35, 50, 48, 49, and 53.” Appeal Brief, page 6 - 7. Appellants reason as follows:

The tables shown in Figs. 2 of the respective Choo references . . . provide designations for only a single finger of a multi-finger zinc finger protein and neither presents a target sequence with three triplets. Although the physical zinc finger proteins, from which the information discussed in the cited references was obtained, may inherently have had three zinc fingers, these physical proteins are not components of a database. If Fig. 2 of either Choo reference is viewed as a database, then the database is composed of the typewritten data in the tables. These typewritten data do

not expressly or inherently contain designations of zinc finger proteins, subdesignations of each of three fingers for each zinc finger protein, or the target sequences of the zinc finger proteins, as claimed. Corbi does nothing to compensate for the[se] deficiencies.

Id., page 7

We agree with Appellants that the cited references do not support a prima facie case of obviousness.

“In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness. Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicant.”

In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993).

The test of obviousness is “whether the teachings of the prior art, taken as a whole, would have made obvious the claimed invention.” In re Gorman, 933 F.2d 982, 986, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991). The claimed invention is the invention defined by all the limitations of the claims. See In re Ochiai, 71 F.3d 1565, 1572, 37 USPQ2d 1127, 1133 (Fed. Cir. 1995) (A proper § 103 analysis requires “a searching comparison of the claimed invention – including all its limitations – with the teaching of the prior art.”).

Here, the claimed method includes, among other things, “providing a database” comprising certain information. Thus, to make out a prima facie case of obviousness, the examiner must show that the prior art would have suggested providing a database that includes the information recited in the claims.

As Appellants point out, the database represented by Figure 2 of Choo (PNAS) does not include all of the information recited in the claims on appeal. The table shows the amino acid sequences of zinc finger regions of fusion proteins based on phage fd coat protein pIII (see Figure 1). Figure 2 of Choo (PNAS) also shows the trinucleotide sequences that are bound by each of the zinc fingers. However, Choo (PNAS) does not provide designations for complete zinc finger proteins that include the zinc fingers shown in Figure 2 or the nucleic acid sequences bound by the complete protein, which must include at least three zinc finger regions to meet the limitations of the claims on appeal. The other cited references also lack a teaching or suggestion of a database including all of the limitations recited in the instant claims.

The examiner responded to Appellants' argument on this point as follows:

Choo et al. [(PNAS)] makes clear in the second column of page 11163 that the library contains variants of a three finger Zif268 protein, and the tables show relevant characteristics of the members of the library. Although Choo et al. [(PNAS)] does not list the entire sequence of each zinc finger protein in the table, the table is nevertheless a table of precharacterized three finger zinc finger proteins as claimed.

Examiner's Answer, page 6.

As we understand it, the examiner's position is that Choo (PNAS) discloses that a phage display library was made that contained a domain made up of three zinc fingers, the middle one of which was varied in order to make fusion proteins that would bind to different trinucleotide sequences, and Table 2 of the reference shows the amino acid sequence of the variant (middle) zinc finger. Thus, the examiner argues, although the table only shows the single, variant zinc finger, the skilled artisan would understand

it to represent an entire zinc finger protein because the rest of the amino acid sequence of each fusion protein was the same.

We agree with the examiner that those skilled in the art would have understood Table 2 of Choo (PNAS) to represent fusion proteins comprising three zinc finger domains: the variant shown in the table and two others that were common to all the members of the library. However, we do not agree that that understanding overcomes the deficiency of the reference.

All of the claims on appeal require the use of a database, not a library of physical compounds, that includes designations for zinc finger proteins that include three zinc finger domains, and “subdesignations for each of the three fingers of each of the zinc finger proteins,” as well as the nucleic acid sequence bound by each of the zinc finger proteins (i.e., the nine-nucleotide long sequence bound by the set of three zinc fingers).

The database disclosed by Choo (PNAS) includes only the information relevant to the middle, variant zinc finger. It does not include subdesignations for the two invariant zinc fingers in each fusion protein, nor does it include the full nucleotide sequence bound by each of the fusion proteins. The cited references therefore do not teach all of the limitations of the claimed method, and the examiner has not adequately explained why a person of ordinary skill in the art would have found it obvious to modify the table/database of Choo (PNAS) to include the additional information.

Summary

The examiner has not shown that the claimed method, including all its limitations, would have been obvious to a person of ordinary skill in the art, based on the cited references. We therefore reverse the rejection of claims 35, 40, 48, 49, and 53.

REVERSED


Demetra J. Mills
Administrative Patent Judge


Eric Grimes
Administrative Patent Judge


Lora M. Green
Administrative Patent Judge

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